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Review

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Abbreviations:
PAH, Pulmonary arterial hypertension; pmVSD, perimembranous Ventricular septal defect; VSD, Ventricular septal defect; LV, Left ventricle; CHD, Congenital Heart Disease; LVEDD, Left ventricle end-diastolic diameter; cAVB, complete Atrio Ventricular Block; FCPC, Filiale de Cardiologie Pediatrique et Congénitale

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Cardiovascular events in perimembranous ventricular septal defect with left ventricular volume overload: a French prospective cohort study (FRANCISCO)

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Brief summary

The long-term prospective multi-centre nationwide (French) observational study FRANCISCO will provide new information on perimembranous ventricular septal defect with left ventricular overload but no pulmonary hypertension in children older than 1 year. Outcomes will be compared according to treatment strategy (watchful waiting, surgical closure, or percutaneous closure) and anatomic features of the defect. The results are expected to provide additional guidance about the optimal treatment of this specific population, which is unclear at present.

Abstract

Background: The management of paediatric isolated perimembranous ventricular septal defect (pmVSD) with left ventricle (LV) volume overload but no pulmonary arterial hypertension (PAH) remains controversial. Three therapeutic approaches are considered: watchful waiting, surgical closure, and percutaneous closure. We aim to investigate the long-term outcomes of these patients according to anatomic pmVSD characteristics and treatment strategy. *Methods:* The *Filiale de Cardiologie Pediatrique et Congénitale* (FCPC) designed the FRANCISCO registry, a long-term prospective nationwide multi-centre observational cohort study sponsored by the French Society of Cardiology, which enrolled, over 2 years (2018–2020), patients older than 1 year who had isolated pmVSD with LV volume overload. Prevalent complications related to pmVSD at baseline were exclusion criteria. Clinical, echocardiographic, and functional data will be collected at inclusion then after 1, 5, and 10 years. A core lab will analyse all baseline echocardiographic data to depict anatomical pmVSD features. The primary outcome is the 5-year incidence of cardiovascular events (infective endocarditis, sub-aortic stenosis, aortic regurgitation, right ventricular outflow tract stenosis, tricuspid regurgitation, PAH, arrhythmia, stroke, haemolysis, heart failure, or death from a cardiovascular event). We plan to enrol 200 patients, given the 10% estimated 5-year incidence of cardiovascular events with a 95% confidence interval of ±5%. Associations linking anatomical pmVSD features and treatment strategy to the incidence of complications will be assessed. *Conclusions:* The FRANSCICO study will provide the long-term incidence of complications in patients older than 1 year with pmVSD and LV volume overload. The results are expected to improve guidance for treatment decisions.

Ventricular septal defect (VSD) is the most common congenital heart defect (CHD), accounting for 30% of cases.[1] Improvements in imaging techniques have increased the recognition of VSD to 50/1000 live births.[2] Perimembranous VSD (pmVSD) accounts for almost 80% of all VSDs in infants older than 1 year.[3–5] pmVSDs are usually located at the anteroseptal commissure behind the septal leaflet of the tricuspid valve and below the commissure of the right and non-coronary leaflets of the aortic valve.[6–8] Four haemodynamic situations can be distinguished: small pmVSD without pulmonary arterial hypertension (PAH) or left ventricle (LV) overload, pmVSD with LV volume overload and reversible PAH, pmVSD with PAH, and pmVSD with LV volume overload but no PAH. Small pmVSDs do not usually cause substantial pulmonary overload or PAH and may close spontaneously in up to a fourth of patients before 1 year of age,[9,10] half the patients before 2 years of age,[11] and 70% of patients before puberty.[12] In contrast, pmVSDs with PAH are usually large defects that cause heart failure in infancy.[13] Consequently, a surgical closure is usually performed within a few months after birth, at a time when the PAH is still reversible.[14,15]

After 1 year of age, small pmVSDs with LV volume overload but no PAH may not require closure since their long-term tolerance is excellent. However, as with all pmVSDs, patients may experience complications including infective endocarditis, aortic regurgitation, and sub-pulmonary or sub-aortic stenosis.[5] Moreover, in adults, long-term LV volume overload may lead to diastolic LV dysfunction and atrial arrhythmias.[16] Therefore, the management of these patients remains controversial. Watchful waiting is usually indicated, but pmVSD closure may be considered in selected cases. The development of new cardiac catheterisation techniques now allows early percutaneous closure.[17] However, difficulties with the first available devices have tempered enthusiasm for this method.[18,19] Thus, the optimal treatment of this category of pmVSD remains unclear.

Our objective was to assess the long-term outcomes of patients with pmVSD and LV volume overload according to the treatment used and to the anatomical characteristics of the pmVSD. To this end, we designed a nationwide multi-centre prospective observational cohort study in France, whose protocol is described here.

Methods

The study will be conducted in compliance with Good Clinical Practices and the Declaration of Helsinki principles. It was approved by a National Ethics Committee (2017-A01396-47). The study is registered on Clinicaltrials.gov (NCT03363932). Written informed consent will be obtained from all participants or their parents or legal guardians before inclusion in the registry.

Study design

The *Filiale de Cardiologie pediatrique et congénitale* (FCPC), which is a branch of the French Society of Cardiology, designed a nationwide, multi-centre, prospective, observational, cohort study (FRANCISCO study). Inclusion occurred over 2 years, from June 2018 to June 2020. Follow-up data will be collected at 1, 5, and 10 years, bringing the total study duration to 12 years.

Patient recruitment

The patients were recruited via the French Network for Complex CHDs (M3C network) and at first-line outpatient cardiology clinics. There are 60 participating centres, and 97 investigators oversaw patient recruitment. The investigators are paediatric cardiologists and adult cardiologists specialised in CHDs.

At each centre, the conduct of the study is led by a local principal investigator, supported, when necessary, by a co-investigator and a clinical research assistant. Each centre is responsible for patient recruitment and follow-up.

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Study patients

Patients older than 1 year with pmVSD and clinically significant LV volume overload were eligible. LV volume overload was defined as an echocardiographic LV end-diastolic diameter z-score (LVEDD) ≥2, according to Kampmann's formula.[20–22]

We did not include patients with prevalent pmVSD-related complications: PAH (mean pulmonary arterial pressure ≥20 mmHg and pulmonary vascular resistance ≥3 UW·m^2)[23–25]; valvular or sub-valvular complications (aortic or pulmonary stenosis with a mean gradient ≥20 mmHg or >grade 2 tricuspid or aortic regurgitation [Laubry-Pezzi syndrome]), history of chronic or persistent atrial arrhythmia or sustained ventricular arrhythmia or high-level atrioventricular block (AVB), active infective endocarditis, or history of heart failure (other than signs related to pulmonary overload during the first year of life).[26] Other exclusion criteria were the concomitant presence of another CHD other than left superior vena cava or right aortic arch and history of open-chest or percutaneous heart interventions.

Data collection

The study data are collected using an electronic care report form (eCRF) at baseline (inclusion) and during follow-up. Patients are identified by an alphanumerical code (FSO followed by eight digits).

At baseline, the following data were collected: demographics, past medical history (endocarditis, bronchiolitis, pulmonary infection, asthma, medical treatment [e.g., diuretics] for overload during the first year of life, growth retardation, stroke, atrial or ventricular premature beats, and associated extracardiac malformations and/or gene mutations or chromosomal anomalies), current weight and height, NYHA or ROSS stage and peripheral oxygen saturation, functional status (6-minute walk test or cardiopulmonary exercise test), electrocardiogram, and blood tests including natriuretic peptides.

Baseline echocardiographic measurements are performed using a standardised approach. All participating sonographers received the same specific training for the study to standardise the recorded views and measurements. Anonymised echocardiographic data were stored off-line and referred for analysis by a core lab. The core lab is composed of three experts in CHD echocardiography and anatomy (M.M.K., L.H., and D.K.) and verified eligibility criteria and VSD characteristics assessable by echocardiography.

The transthoracic echocardiographic assessment included a standardised anatomical echocardiogram,[27] LV end-diastolic diameter measurement on M mode images, aortic root and left atrial diameters, systolic and diastolic function parameters of the right and left ventricles, and pmVSD morphology (systolic aorto-septal angulation, presence of a septal aneurysm, systolic and diastolic diameters of the functional defect, number of defects, distance between the defect and the aortic cusp in diastole, superior or inferior extension of the pmVSD, and aortic cusp anomalies).

Follow-up data collected 1, 5, and 10 years after enrolment include clinical status, function (6-minute walk test, exercise tests), and echocardiographic parameters. Neurodevelopmental outcomes will be assessed at 5 and 10 years using the double-sided Strengths and Difficulties Questionnaire. The referral cardiologist determines whether watchful waiting or surgical or percutaneous pmVSD closure is optimal. The patients will have an annual follow-up with clinical, functional, and echocardiographic evaluation.

The following cardiovascular events are collected: infective endocarditis, development of aortic stenosis (mean gradient >20 mmHg) or aortic regurgitation, right ventricular outflow tract stenosis (mean gradient >20 mmHg), tricuspid regurgitation ≥grade 2, PAH development, heart surgery or percutaneous heart procedure related to the pmVSD, persistent or chronic atrial arrhythmia or sustained ventricular arrhythmia, complete atrioventricular block (cAVB), severe haemolysis, heart failure, stroke, or death from a cardiovascular cause. The composite of these events at 5 years is the primary outcome. In patients who underwent percutaneous or surgical closure, details on the procedures are collected.

Sample size estimation

The estimated incidence of cardiovascular events is 10% at 5 years. Consequently, 200 patients will be needed to reach a 95% confidence interval (95%CI) of ±5%.

Statistical analysis

The baseline variables in the population will be described as mean ± SD if the distribution is normal and as median [interquartile range] otherwise. The anatomical features of pmVSD will be depicted. The incidence of the composite cardiovascular events at 5 and 10 years will be determined for the overall population and in sub-groups defined by anatomical features at baseline and by the treatment strategy. In addition, the incidence of each component of the composite criterion will be determined. Event-free survival curves will be constructed using the Kaplan–Meier method and compared among sub-groups using the log-rank test. The annualised incidence will be calculated. We will also look for risk factors for cardiovascular events in this population, using Cox models. The impact of genetic syndromes, chromosomal abnormalities, or significant extracardiac abnormalities will also be analysed.

Study outcomes

The primary outcome is the 5-year incidence of the composite criterion of cardiovascular events described above.

Anatomical features associated with the primary outcome will be sought. The 1-year changes in echocardiographic and functional parameters in each treatment sub-group will be compared. The incidence of cardiovascular events in the different treatment groups will be evaluated at 5 and 10 years.

Discussion

To our knowledge, the FRANCISCO registry is the first long-term prospective multi-centre source of data on children who have isolated pmVSD with LV volume overload but no PAH. While the treatment of muscular, outlet, and inlet VSDs is well standardised,[1,13] the management of pmVSD remains controversial. No clear guidelines exist about the indications for closure in patients who have asymptomatic isolated pmVSD with LV volume overload but no PAH. It has been suggested that closure of small pmVSDs may be warranted if Qp/Qs exceeds 1.5 or if echocardiography shows left atrial or ventricular dilation.[9,32,33] Paediatric cardiology textbooks still advise VSD closure when Qp/Qs exceeds 2, but the indications have changed for adults. Many studies have reported delayed complications in patients who have asymptomatic unrepaired VSD with LV volume overload but no PAH.[16,28,29] We estimated that the cumulative incidence of events will rise 10% at 10 years, but there is a lack of data to support this assertion on this specific sub-type of VSD. These studies are biased

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by heterogeneity regarding the anatomical and physiological types of VSDs in the included patients. Thus, the incidence of complications in the specific population of patients who have pmVSD with LV volume overload but no PAH is still unknown. We, therefore, expect that our prospective study focusing on this specific population will provide new insights into the occurrence of long-term cardiovascular complications.

Furthermore, the exact definition of cardiac volume overload determined using non-invasive means in this population remains unclear in most studies. Recently, non-invasive echocardiographic measurements of LVEDD z-score values have been identified as reliable for diagnosing and monitoring LV volume overload. Thus, the FRANCISCO study will bring more accurate information on the incidence and type of complications in patients with pmVSD who meet the LVEDD z-score criterion for LV volume overload.[20–22]

Currently, pmVSD with LV volume overload but no PAH is managed either by watchful waiting or by closure, depending on the clinical symptoms and practice patterns at each centre. The closure is often advocated to avoid late LV dysfunction related to cardiac volume overload. However, this complication has not been well described. Other complications of long-term VSD shunting are infective endocarditis, valvular or sub-valvular complications, heart failure, and arrhythmias. The incidence of infective endocarditis was about 1.8% (n = 4) in a cohort of 222 patients with unrepaired VSD aged 30 ± 10 years at last follow-up[5]; 2 of the 4 patients required aortic valve replacement. Aortic regurgitation by aortic cusp prolapse due to the Venturi effect (Laubry-Pezzi syndrome),[30] pulmonary or aortic stenosis, and tricuspid regurgitation have been reported in 21, 6, and 3.7%, respectively, of patients with unrepaired pmVSD.[11,13,16,31,32] In the retrospective Belgian pmVSD registry of adults, aortic regurgitation affected 21% of patients with unrepaired pmVSD.[16] However, in these studies, the relationship of complications with the shunt volume was not assessed. Severe shunting and anatomical characteristics such as the aorto-septal angulation may be linked to the occurrence of sub-valvular complications.[33] Moreover, the anatomical features of the sub-aortic rim seem to have a major influence on the feasibility of percutaneous closure. The FRANCISCO study will obtain details on this point, as the echocardiographic core lab will specifically analyse the anatomical features of pmVSD and their associations with outcomes.

Dilation of the left atrium and LV is associated with the occurrence of heart failure and arrhythmias. Paroxysmal atrial arrhythmia has been reported in 1–3% of patients,[16] and heart failure in less than 5%. Some reports suggest that a long-standing VSD may lead to disturbed diastolic function and decreased compliance of both ventricles.[34] Eisenmenger syndrome has been reported in 15 (6%) of 266 patients with pmVSD,[16] with risk factors being Down syndrome and large VSD size. However, the occurrence of PAH during the follow-up of patients who have pmVSD with LV volume overload but no PAH is unusual, although the exact incidence is unknown. Our study may also offer new information on this point. Overall, the incidence of complications in patients with unrepaired pmVSD followed up for more than 1 year is considered to be low, and prophylactic pmVSD closure remains controversial in France for pmVSD with LV enlargement but no PAH, as the benefits may not outweigh the risks of surgical or percutaneous closure.[35]

Watchful waiting is supported by the good tolerance of the shunt after 1 year of age. Moreover, there is evidence that shunt severity and LV dilation tend to decrease after 1 year.[12,36] LVEDD z-score values decreased in 29 (88%) of 33 patients with LV volume overload, falling below 2 in 26 (79%) patients.[12] The FRANCISCO study will provide additional data in a larger population by assessing the functional status and LVEDD z-score changes during follow-up.

Another argument in favour of watchful waiting is that surgical or percutaneous closure carries risks. Despite recent advances in paediatric cardiac catheterisation and surgery, pmVSD closure remains a complex invasive procedure given the close relationship of the defect with the aortic and tricuspid valves and conduction pathway. However, currently, surgical closure of isolated VSD is effective, rarely results in complications, and has a mortality rate of less than 1%.[37,38] One of the complications of greatest concern is cAVB, which has been reported in less than 1% of children[38] Long-term morbidity after surgical VSD closure has also been assessed. In 174 patients with 40 years' follow-up after VSD closure, mortality was not significantly different from that in the general population.[39] However, the event-free survival rate was significantly lower than in the general population.[40] Symptomatic arrhythmia, heart failure, and infective endocarditis occurred in 11, 4, and 3% of patients.[39] The most frequent complication was mild-to-moderate aortic regurgitation, which developed in 21% of patients. In the Belgian registry, pmVSD closure was followed by atrial arrhythmias in 4% and by cAVB requiring pacemaker implantation in 4% of patients.[16] The need to perform a right atriotomy contributes to the occurrence of re-entrant intra-atrial arrhythmias. In patients who had had surgical closure in early childhood and were evaluated in young adulthood, peak oxygen uptake, ventilatory anaerobic threshold, maximal workload, and peak heart rate were lower compared to those in controls.[41] However, myocardial protection and post-operative care have improved substantially over time, and VSD closure is now rarely performed at a very early age. The FRANCISCO study will supply prospective follow-up data on the incidence of complications and changes in functional status in patients with pmVSD and LV volume overload managed by surgical closure versus watchful waiting.

Systematic reviews and meta-analyses have established that transcatheter VSD closure is feasible using a coil or occluder. A pooled estimate of successful device implantation of about 96.6% has been reported.[42,43] However, residual shunting, valvular defects, arrhythmias, and early or delayed cAVB were observed in some cases. Reports of cAVB both during the procedure and during long-term follow-up with the first Amplatzer device put a halt to its widespread use. A substantial rate of severe haemolysis related to residual shunting has limited the use of coils.[44] Softer occluders are being developed and may be of interest, although strong clinical evidence will need to be obtained before considering their widespread use.[45–47] The newest devices seem to carry a lower risk of cAVB, but follow-ups remain short and cAVB may be delayed for several years.[18,48,49] In most centres in France, a surgical closure is the preferred method when the closure is indicated. The FRANCISCO study will also determine the potential influence of anatomical pmVSD features on the safety of percutaneous closure and may help to design new and safer devices.

Although some meta-analyses and reviews have assessed the risk/benefit ratio of percutaneous versus surgical pmVSD closure, most studies were retrospective and did not specifically include patients older than 1 year with LV volume overload but no PAH. The FRANCISCO study will provide new answers about the management of this specific population. We also expect to

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identify anatomical features that predict complications. We acknowledge that a randomised controlled trial would provide a higher level of evidence about the respective merits of current treatment options. Nevertheless, given the small number and heterogeneity of current guidelines, our prospective cohort reflecting current practices in an industrialised country will offer useful data to guide therapeutic decisions.

Conclusion

The management of patients with pmVSD and LV dilatation but no PAH varies across centres and countries. The prospective French nationwide FRANCISCO cohort study will provide information on the long-term incidence of cardiovascular events in patients older than 1 year who have pmVSD and LV volume overload but no PAH. Risk factors for events, such as anatomical pmVSD features and treatment strategy, will be assessed. We expect the results of the study to provide new information for guiding treatment decisions.

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Conflict of interest. None.

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